

UNITED STATES PATENT APPLICATION

OF

STEPHEN HUNTER DIAZ

FOR

METHOD AND APPARATUS FOR LOADING A
BENEFICIAL AGENT INTO AN EXPANDABLE MEDICAL DEVICE

Attorney Docket No. 032304-076
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300

**METHOD AND APPARATUS FOR LOADING
A BENEFICIAL AGENT INTO AN EXPANDABLE MEDICAL DEVICE**

Cross-Reference to Related Applications

[0001] This application is a continuation-in-part of U.S. Utility Patent Application Serial No. 10/447,587, filed on May 28, 2003, which is incorporated herein by reference in its entirety. This application also claims priority to U.S. Provisional Patent Application Serial No. 60/412,489, filed on September 20, 2002, which is incorporated herein by reference in its entirety.

Field of the Invention

[0002] The invention relates to a method and apparatus for loading a beneficial agent, such as a drug into an expandable medical device, and more particularly, the invention relates to a method and apparatus for dispensing a beneficial agent into an expandable medical device such as a stent.

Description of the Related Art

[0003] Implantable medical devices are often used for delivery of a beneficial agent, such as a drug, to an organ or tissue in the body at a controlled delivery rate over an extended period of time. These devices may deliver agents to a wide variety of bodily systems to provide a wide variety of treatments.

[0004] One of the many implantable medical devices which have been used for local delivery of beneficial agents is the coronary stent. Coronary stents are typically introduced percutaneously, and transported transluminally until positioned at a desired location. These devices are then expanded either

mechanically, such as by the expansion of a mandrel or balloon positioned inside the device, or expand themselves by releasing stored energy upon actuation within the body. Once expanded within the lumen, these devices, called stents, become encapsulated within the body tissue and remain a permanent implant.

[0005] Known stent designs include monofilament wire coil stents (U.S. Pat. No. 4,969,458); welded metal cages (U.S. Pat. Nos. 4,733,665 and 4,776,337); and, most prominently, thin-walled metal cylinders with axial slots formed around the circumference (U.S. Pat. Nos. 4,733,665; 4,739,762; and 4,776,337). Known construction materials for use in stents include polymers, organic fabrics and biocompatible metals, such as stainless steel, gold, silver, tantalum, titanium, and shape memory alloys, such as Nitinol.

[0006] Of the many problems that may be addressed through stent-based local delivery of beneficial agents, one of the most important is restenosis. Restenosis is a major complication that can arise following vascular interventions such as angioplasty and the implantation of stents. Simply defined, restenosis is a wound healing process that reduces the vessel lumen diameter by extracellular matrix deposition, neointimal hyperplasia, and vascular smooth muscle cell proliferation, and which may ultimately result in renarrowing or even reocclusion of the lumen. Despite the introduction of improved surgical techniques, devices, and pharmaceutical agents, the overall restenosis rate is still reported in the range of 25% to 50% within six to twelve months after an angioplasty procedure. To treat this condition, additional revascularization procedures are frequently required, thereby increasing trauma and risk to the patient.

[0007] One of the techniques under development to address the problem of restenosis is the use of surface coatings of various beneficial agents on stents. U.S. Pat. No. 5,716,981, for example, discloses a stent that is surface-coated with a composition comprising a polymer carrier and paclitaxel (a well-known

compound that is commonly used in the treatment of cancerous tumors). The patent offers detailed descriptions of methods for coating stent surfaces, such as spraying and dipping, as well as the desired character of the coating itself: it should “coat the stent smoothly and evenly” and “provide a uniform, predictable, prolonged release of the anti-angiogenic factor.” Surface coatings, however, can provide little actual control over the release kinetics of beneficial agents. These coatings are necessarily very thin, typically 5 to 8 microns deep. The surface area of the stent, by comparison is very large, so that the entire volume of the beneficial agent has a very short diffusion path to discharge into the surrounding tissue.

[0008] Increasing the thickness of the surface coating has the beneficial effects of improving drug release kinetics including the ability to control drug release and to allow increased drug loading. However, the increased coating thickness results in increased overall thickness of the stent wall. This is undesirable for a number of reasons, including increased trauma to the vessel wall during implantation, reduced flow cross-section of the lumen after implantation, and increased vulnerability of the coating to mechanical failure or damage during expansion and implantation. Coating thickness is one of several factors that affect the release kinetics of the beneficial agent, and limitations on thickness thereby limit the range of release rates, duration of drug delivery, and the like that can be achieved.

[0009] In addition to sub-optimal release profiles, there are further problems with surface coated stents. The fixed matrix polymer carriers frequently used in the device coatings typically retain approximately 30% or more of the beneficial agent in the coating indefinitely. Since these beneficial agents are frequently highly cytotoxic, sub-acute and chronic problems such as chronic inflammation, late thrombosis, and late or incomplete healing of the vessel wall may occur. Additionally, the carrier polymers themselves are often highly inflammatory to the

tissue of the vessel wall. On the other hand, use of biodegradable polymer carriers on stent surfaces can result in the creation of “virtual spaces” or voids between the stent and tissue of the vessel wall after the polymer carrier has degraded, which permits differential motion between the stent and adjacent tissue. Resulting problems include micro-abrasion and inflammation, stent drift, and failure to re-endothelialize the vessel wall.

[0010] Another significant problem is that expansion of the stent may stress the overlying polymeric coating causing the coating to plastically deform or even to rupture, which may therefore effect drug release kinetics or have other untoward effects. Further, expansion of such a coated stent in an atherosclerotic blood vessel will place circumferential shear forces on the polymeric coating, which may cause the coating to separate from the underlying stent surface. Such separation may again have untoward effects including embolization of coating fragments causing vascular obstruction.

[0011] In addition, it is not currently possible to deliver some drugs with a surface coating due to sensitivity of the drugs to water, other compounds, or conditions in the body which degrade the drugs. For example, some drugs lose substantially all their activity when exposed to water for a period of time. When the desired treatment time is substantially longer than the half life of the drug in water, the drug cannot be delivered by known coatings. Other drugs, such as protein or peptide based therapeutic agents, lose activity when exposed to enzymes, pH changes, or other environmental conditions. These drugs which are sensitive to compounds or conditions in the body often cannot be delivered using surface coatings.

[0012] Accordingly, it would be desirable to provide an apparatus and method for loading a beneficial agent into an expandable medical device, such as a stent, for delivery of agents, such as drugs, to a patient.

Summary of the Invention

[0013] The present invention relates to an apparatus and method for loading a beneficial agent in an expandable medical device.

[0014] In accordance with one aspect of the invention, a method for loading a medical device with a beneficial agent includes the steps of providing a medical device with a plurality of holes, dispensing a beneficial agent through a dispenser into the plurality of holes by vibration of a portion of the dispenser to form a plurality of droplets, and controlling a size of the droplets by controlling parameters of the vibration.

[0015] In accordance with a further aspect of the invention, a method for loading a medical device with a beneficial agent includes the steps of providing a medical device to be provided with a therapeutic agent, providing a dispenser containing a beneficial agent including a therapeutic agent and a volatile solvent, delivering droplets of the beneficial agent to the medical device with the dispenser, and inhibiting evaporation of the volatile solvent during delivery of the droplets by creating a cloud of vaporized solvent around an exit orifice of the dispenser.

[0016] In accordance with another aspect of the invention, a system for loading a medical device with a beneficial agent comprises a mandrel for supporting a medical device, a dispenser for dispensing a beneficial agent into a plurality of holes in the medical device by vibration of a portion of the dispenser, and a central processing unit for controlling a size of droplets of beneficial agent from the dispenser by controlling parameters of the vibration.

Brief Description of the Drawing Figures

[0017] The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings, in which like

elements bear like reference numerals, and wherein:

[0018] FIG. 1 is a perspective view of a therapeutic agent delivery device in the form of an expandable stent.

[0019] FIG. 2 is a cross-sectional view of a portion of a therapeutic agent delivery device having a beneficial agent contained in an opening in layers.

[0020] FIG. 3 is a side view of a piezoelectric micro-jetting dispenser for delivery of a beneficial agent.

[0021] FIG. 4 is a cross-sectional view of an expandable medical device on a mandrel and a piezoelectric micro-jetting dispenser.

[0022] FIG. 5 is a perspective view of a system for loading an expandable medical device with a beneficial agent.

[0023] FIG. 6 is a perspective view of a bearing for use with the system of FIG. 5.

[0024] FIG. 7 is a side cross-sectional view of an acoustic dispenser for delivery of a beneficial agent to an expandable medical device.

[0025] FIG. 8 is a side cross-sectional view of an alternative acoustic dispenser reservoir.

[0026] FIG. 9 is a side cross-sectional view of an alternative piezoelectric dispenser system.

Detailed Description of the Invention

[0027] The present invention relates to a method and apparatus for loading a beneficial agent into an expandable medical device. More particularly, the invention relates to a method and apparatus for loading a beneficial agent in a stent.

[0028] First, the following terms, as used herein, shall have the following meanings:

[0029] The term "beneficial agent" as used herein is intended to have its broadest possible interpretation and is used to include any therapeutic agent or drug, as well as inactive agents such as barrier layers, carrier layers, therapeutic layers or protective layers.

[0030] The terms "drug" and "therapeutic agent" are used interchangeably to refer to any therapeutically active substance that is delivered to a bodily conduit of a living being to produce a desired, usually beneficial, effect. The present invention is particularly well suited for the delivery of antineoplastic, angiogenic factors, immuno-suppressants, anti-inflammatories and antiproliferatives (anti-restenosis agents) such as paclitaxel and Rapamycin for example, and antithrombins such as heparin, for example.

[0031] The term "matrix" or "biocompatible matrix" are used interchangeably to refer to a medium or material that, upon implantation in a subject, does not elicit a detrimental response sufficient to result in the rejection of the matrix. The matrix typically does not provide any therapeutic responses itself, though the matrix may contain or surround a therapeutic agent, a therapeutic agent, an activating agent or a deactivating agent, as defined herein. A matrix is also a medium that may simply provide support, structural integrity or structural barriers. The matrix may be polymeric, non-polymeric, hydrophobic, hydrophilic, lipophilic, amphiphilic, and the like.

[0032] The term "bioresorbable" refers to a matrix, as defined herein, that can be broken down by either chemical or physical process, upon interaction with a physiological environment. The bioresorbable matrix is broken into components that are metabolizable or excretable, over a period of time from minutes to years, preferably less than one year, while maintaining any requisite structural integrity in that same time period.

[0033] The term "polymer" refers to molecules formed from the chemical union

of two or more repeating units, called monomers. Accordingly, included within the term "polymer" may be, for example, dimers, trimers and oligomers. The polymer may be synthetic, naturally-occurring or semisynthetic. In preferred form, the term "polymer" refers to molecules which typically have a M_w greater than about 3000 and preferably greater than about 10,000 and a M_w that is less than about 10 million, preferably less than about a million and more preferably less than about 200,000.

[0034] The term "openings" refers to holes of any shape and includes both through-openings and recesses.

Implantable Medical Devices with Holes

[0035] FIG. 1 illustrates a medical device 10 according to the present invention in the form of a stent design with large, non-deforming struts 12 and links 14, which can contain openings (or holes) 20 without compromising the mechanical properties of the struts or links, or the device as a whole. The non-deforming struts 12 and links 14 may be achieved by the use of ductile hinges which are described in detail in U.S. Patent No. 6,241,762 which is incorporated hereby by reference in its entirety. The holes 20 serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site.

[0036] As shown in FIG. 1, the openings 20 can be circular 22, rectangular 24, or D-shaped 26 in nature and form cylindrical, rectangular, or D-shaped holes extending through the width of the medical device 10. It can be appreciated that the openings 20 can be other shapes without departing from the present invention.

[0037] The volume of beneficial agent that can be delivered using openings 20 is about 3 to 10 times greater than the volume of a 5 micron coating covering a stent with the same stent/vessel wall coverage ratio. This much larger beneficial agent capacity provides several advantages. The larger capacity can be used to deliver

multi-drug combinations, each with independent release profiles, for improved efficacy. Also, larger capacity can be used to provide larger quantities of less aggressive drugs and to achieve clinical efficacy without the undesirable side-effects of more potent drugs, such as retarded healing of the endothelial layer.

[0038] FIG. 2 shows a cross-section of a medical device 10 in which one or more beneficial agents have been loaded into the opening 20 in layers. Examples of some methods of creating such layers and arrangements of layers are described in U.S. Patent Application No. 09/948,989, filed on September 7, 2001, which is incorporated herein by reference in its entirety. Although the layers are illustrated as discrete layers, the layers can also mix together upon delivery to result in an inlay of beneficial agent with concentration gradients of therapeutic agents but without distinct boundaries between layers.

[0039] According to one example, the total depth of the opening 20 is about 100 to about 140 microns, typically 125 microns and the typical layer thickness would be about 2 to about 50 microns, preferably about 12 microns. Each typical layer is thus individually about twice as thick as the typical coating applied to surface-coated stents. There would be at least two and preferably about ten to twelve such layers in a typical opening, with a total beneficial agent thickness about 25 to 28 times greater than a typical surface coating. According to one preferred embodiment of the present invention, each of the openings have an area of at least 5×10^{-6} square inches, and preferably at least 7×10^{-6} square inches. Typically, the openings are filled about 50% to about 75% full of beneficial agent.

[0040] Since each layer is created independently, individual chemical compositions and pharmacokinetic properties can be imparted to each layer. Numerous useful arrangements of such layers can be formed, some of which will be described below. Each of the layers may include one or more agents in the same or different proportions from layer to layer. The layers may be solid,

porous, or filled with other drugs or excipients. As mentioned above, although the layers are deposited separately, they may mix forming an inlay without boundaries between layers.

[0041] As shown in FIG. 2, the opening 20 is filled with a beneficial agent. The beneficial agent includes a barrier layer 40, a therapeutic layer 30, and a cap layer 50.

[0042] Alternatively, different layers could be comprised of different therapeutic agents altogether, creating the ability to release different therapeutic agents at different points in time. The layers of beneficial agent provide the ability to tailor a delivery profile to different applications. This allows the medical device according to the present invention to be used for delivery of different beneficial agents to a wide variety of locations in the body.

[0043] A protective layer in the form of a cap layer 50 is provided at a tissue contacting surface of a medical device. The cap layer 50 can block or retard biodegradation of subsequent layers and/or blocks or retards diffusion of the beneficial agent in that direction for a period of time which allows the delivery of the medical device to a desired location in the body. When the medical device 10 is a stent which is implanted in a lumen, the barrier layer 40 is positioned on a side of the opening 20 facing the inside of the lumen. The barrier layer 40 prevents the therapeutic agent 30 from passing into the lumen and being carried away without being delivered to the lumen tissue.

[0044] Typical formulations for therapeutic agents incorporated in these medical devices are well known to those skilled in the art.

Uses for Implantable Medical Devices

[0045] Although the present invention has been described with reference to a medical device in the form of a stent, the medical devices of the present invention

can also be medical devices of other shapes useful for site-specific and time-release delivery of drugs to the body and other organs and tissues. The drugs may be delivered to the vasculature including the coronary and peripheral vessels for a variety of therapies, and to other lumens in the body. The drugs may increase lumen diameter, create occlusions, or deliver the drug for other reasons.

[0046] Medical devices and stents, as described herein, are useful for the prevention of amelioration of restenosis, particularly after percutaneous transluminal coronary angioplasty and intraluminal stent placement. In addition to the timed or sustained release of anti-restenosis agents, other agents such as anti-inflammatory agents may be incorporated into the multi-layers incorporated in the plurality of holes within the device. This allows for site-specific treatment or prevention any complications routinely associated with stent placements that are known to occur at very specific times after the placement occurs.

Methods and Systems for Loading a Beneficial Agent in a Medical Device

[0047] FIG. 3 shows a piezoelectric micro-jetting dispenser 100 used to dispense a beneficial agent into the opening of a medical device. The dispenser 100 has a capillary tube 108 having a fluid outlet or orifice 102, a fluid inlet 104, and an electrical cable 106. The piezoelectric dispenser 100 preferably includes a piezo crystal 110 within a housing 112 for dispensing a fluid droplet through the orifice 102. The crystal 110 surrounds a portion of the capillary tube 108 and receives an electric charge that causes the crystal to vibrate. When the crystal vibrates inward, it forces a tiny amount of fluid out of the fluid outlet 102 of the tube 108 to fill an opening 20 in a medical device. In addition, when the crystal vibrates outward, the crystal pulls additional fluid into the tube 108 from a fluid reservoir connected to the inlet 104 to replace the fluid that has been dispensed into the opening of the medical device.

[0048] In one embodiment as shown in FIG. 3, the micro-jetting dispenser 100 includes an annular piezoelectric (PZT) actuator 110 bonded to a glass capillary 108. The glass capillary 108 is connected at one end to a fluid supply (not shown) and at the other end has an orifice 102 generally in the range of about .5 to about 150 microns, and more preferably about 30 to about 60 microns. When a voltage is applied to the PZT actuator, the cross-section of the capillary glass 108 is reduced/increased producing pressure variations of the fluid enclosed in the glass capillary 108. These pressure variations propagate in the glass capillary 108 toward the orifice 102. The sudden change in cross-section (acoustic impedance) at the orifice 102, causes a droplet to be formed. This mode of producing droplets is generally called drop on demand (DOD).

[0049] In operation, the micro-jetting dispenser 100, depending on the viscosity and contact angle of the fluid, can require either positive or negative pressure at the fluid inlet 104. Typically, there are two ways to provide pressure at the fluid inlet 104. First, the pressure at the fluid inlet 104 can be provided by either a positive or a negative head by positioning of the fluid supply reservoir. For example, if the fluid reservoir is mounted only a few millimeters above the dispenser 100, a constant positive pressure will be provided. However, if the fluid reservoir is mounted a few millimeters below the dispenser 100, the orifice 102 will realize a negative pressure.

[0050] Alternatively, the pressure of the fluid at the inlet 104 can be regulated using existing compressed air or vacuum sources. For example, by inserting a pressure vacuum regulator between the fluid source and the dispenser 100, the pressure can be adjusted to provide a constant pressure flow to the dispenser 100.

[0051] In addition, a wide range of fluids including beneficial agents can be dispensed through the dispenser 100. The fluids delivered by the dispenser 100 preferably have a viscosity of no greater than about 40 centipoise. The droplet

volume of the dispenser 100 is a function of the fluid, orifice 102 diameter, and actuator driving parameter (voltage and timing) and usually ranges from about 50 picoliters to about 200 picoliters per droplet. If a continuous droplet generation is desired, the fluid can be pressurized and a sinusoidal signal applied to the actuator to provide a continuous jetting of fluids. Depending on the beneficial agent dispensed, each droplet may appear more like a filament.

[0052] It can be appreciated that other fluid dispensing devices can be used without departing from the present invention. In one embodiment, the dispenser is a piezoelectric micro-jetting device manufactured by MicroFab Technologies, Inc., of Plano, Texas. Other examples of dispensers will be discussed below with respect to FIGS. 7-9.

[0053] The electric cable 106 is preferably connected to associated drive electronics (not shown) for providing a pulsed electric signal. The electric cable 106 provides the electric signal to control the dispensing of the fluid through the dispenser 100 by causing the crystal to vibrate.

[0054] FIG. 4 shows an expandable medical device in the form of a stent 140 receiving a droplet 120 of a beneficial agent from a piezoelectric micro-jetting dispenser 100. The stent 140 is preferably mounted to a mandrel 160. The stent 140 can be designed with large, non-deforming struts and links (as shown in FIG. 1), which contain a plurality of openings 142 without compromising the mechanical properties of the struts or links, or the device as a whole. The openings 142 serve as large, protected reservoirs for delivering various beneficial agents to the device implantation site. The openings 142 can be circular, rectangular, or D-shaped in nature and form cylindrical, rectangular or D-shaped holes extending through the width of the stent 140. In addition, openings 142 having a depth less than the thickness of the stent 140 may also be used. It can be

appreciated that other shaped holes 142 can be used without departing from the present invention.

[0055] The volume of the hole 142 will vary depending on the shape and size of the hole 142. For example, a rectangular shaped opening 142 having a width of .1520 mm (.006 inches) and a height of .1270 mm (.005 inches) will have a volume of about 2.22 nanoliters. Meanwhile, a round opening having a radius of .0699 mm (.00275 inches) will have a volume of about 1.87 nanoliters. A D-shaped opening having a width of .1520 mm (.006 inches) along the straight portion of the D, has a volume of about 2.68 nanoliters. The openings according to one example are about .1346 mm (.0053 inches) in depth having a slight conical shape due to laser cutting.

[0056] Although a tissue supporting device configuration has been illustrated in FIG. 1, which includes ductile hinges, it should be understood that the beneficial agent may be contained in openings in stents having a variety of designs including many of the known stents.

[0057] The mandrel 160 can include a wire member 162 encapsulated by an outer jacket 164 of a resilient or a rubber-like material. The wire member 162 may be formed from a metallic thread or wire having a circular cross-section. The metallic thread or wire is preferably selected from a group of metallic threads or wire, including Nitinol, stainless steel, tungsten, nickel, or other metals having similar characteristics and properties.

[0058] In one example, the wire member 162 has an outer diameter of between about .889 mm (.035 inches) and about .991 mm (.039 inches) for use with a cylindrical or implantable tubular device having an outer diameter of about 3 mm (.118 inches) and an overall length of about 17 mm (.669 inches). It can be appreciated that the outer diameter of the wire member 162 will vary depending on the size and shape of the expandable medical device 140.

[0059] Examples of rubber-like materials for the outer jacket 164 include silicone, polymeric materials, such as polyethylene, polypropylene, polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyurethane, polyamides, polyethylene terephthalate (PET), and their mixtures and copolymers. However, it can be appreciated that other materials for the outer jacket 164 can be implemented, including those rubber-like materials known to those skilled in the art.

[0060] In one embodiment, the wire member 162 is encapsulated in a tubular outer jacket 164 having an inner diameter of about .635 mm (0.25 inches). The outer jacket 164 can be mounted over the wire member 162 by inflating the tubular member to increase to a size greater than the outer diameter of the wire member 162. The tubular member can be inflated using an air pressure device known to those skilled in the art. The wire member 162 is placed inside of the outer jacket 164 by floating the outer jacket 164 of silicon over the wire member 162. However, it can be appreciated that the wire member 162 can be encapsulated in an outer jacket of silicon or other rubber-like material by any method known to one skilled in the art.

[0061] In one embodiment for loading stents having a diameter of about 3 mm (.118 inches) and a length of about 17 mm (.669 inches), a wire member 162 having an outer diameter of .939 mm (.037 inches) is selected. In one example, the wire member 162 is about 304.8 mm (12 inches) in length. The outer jacket 164 has an inner diameter of about .635 mm (.025 inches).

[0062] The expandable medical device or stent 140 is then loaded onto the mandrel 160 in any method known to one skilled in the art. In one embodiment, the stents 140 and the mandrel 160 are dipped into a volume of lubricant to lubricate the stents 140 and the mandrel 160. The stents 140 are then loaded onto the mandrel 160. The drying of the stents 140 and the mandrel 160 create a

substantially firm fit of the stents 140 onto the mandrel 160. Alternatively, or in addition to drying, the stents 140 can be crimped onto the mandrel by a method known to one skilled in the art onto the mandrel 160. The crimping ensures that the stents 140 will not move or rotate during mapping or filling of the openings.

[0063] FIG. 5 shows a system 200 for loading a beneficial agent in an expandable medical device. The system 200 includes a dispenser 210 for dispensing a beneficial agent into an opening of an expandable medical device, a reservoir of beneficial agent 218 at least one observation system 220, and a mandrel 230 having a plurality of expandable medical devices 232 attached to the mandrel 230. The system 200 also includes a plurality of bearings 240 for supporting the rotating mandrel 230, a means for rotating and translating the mandrel 250 along a cylindrical axis of the expandable medical device 232, a monitor 260, and a central processing unit (CPU) 270.

[0064] The dispenser 210 is preferably a piezoelectric dispenser for dispensing a beneficial agent into the opening in the medical device 232. The dispenser 210 has a fluid outlet or orifice 212, a fluid inlet 214 and an electrical cable 216. The piezoelectric dispenser 200 dispenses a fluid droplet through the orifice 212.

[0065] At least one observation system 220 is used to observe the formation of the droplets and the positioning of the dispenser 210 relative to the plurality of openings in the medical device 232. The observation system 220 may include a charge coupled device (CCD) camera. In one embodiment, at least two CCD cameras are used for the filling process. The first camera can be located above the micro-jetting dispenser 210 and observes the filling of the medical device 232. The first camera is also used for mapping of the mandrel 230 as will be described below. A second camera is preferably located on a side of the micro-jetting dispenser 210 and observes the micro-jetting dispenser 210 from a side or orthogonal view. The second camera is preferably used to visualize the micro-

jetting dispenser during the positioning of the dispenser before loading of the medical device 232 with a beneficial agent. However, it can be appreciated that the observation system 220 can include any number of visualization systems including a camera, a microscope, a laser, machine vision system, or other known device to one skilled in the art. For example, refraction of a light beam can be used to count droplets from the dispenser. The total magnification to the monitor should be in the range of 50 to 100 times.

[0066] In one embodiment, a LED synchronized light 224 with the PZT pulse provides lighting for the system 200. The delay between the PZT pulse and the LED pulse is adjustable, allowing the capture of the droplet formation at different stages of development. The observation system 220 is also used in mapping of the mandrel 230 and medical devices 232 for loading of the openings. In one embodiment, rather than using a LED synchronized light 224, the lighting is performed using a diffused fluorescent lighting system. It can be appreciated that other lighting systems can be used without departing from the present invention.

[0067] A plurality of expandable medical devices 232 are mounted to the mandrel 230 as described above. For example, a mandrel which is about 12 inches in length can accommodate about 11 stents having a length of about 17 mm each. Each mandrel 230 is labeled with a bar code 234 to ensure that each mandrel is properly identified, mapped, and then filled to the desired specifications.

[0068] The mandrel 230 is positioned on a plurality of bearings 240. As shown in FIG. 6, one example of the bearings 240 have a V-shaped notch 242. The mandrel 230 is positioned within the V-shaped notch 242 and secured using a clip 244. The clip 244 is preferably a coil spring, however, other means of securing the mandrel within the V-shaped notch can be used including any type of clip or securing means can be used. The bearings 240 can be constructed of a metallic

material, preferably different than the mandrel wire, such as stainless steel, copper, brass, or iron.

[0069] The mandrel 230 is connected to a means for rotating and translating the mandrel 250 along the cylindrical axis of the medical device 232. The means for rotating and translating the mandrel 250 can be any type or combination of motors or other systems known to one skilled in the art.

[0070] In one embodiment, the mandrel 250 and medical device 232 are moved from a first position to a second position to fill the openings of the medical device 232 with the beneficial agent. In an alternative embodiment, the system further includes a means for moving the dispensing system along the cylindrical axis of the medical device 232 from a first position to a second position.

[0071] A monitor 260 is preferably used to observe the loading of the medical device 232 with a beneficial agent. It can be appreciated that any type of monitor or other means of observing the mapping and loading process can be used.

[0072] A central processing unit 270 (or CPU) controls the loading of the medical device 232 with the beneficial agent. The CPU 270 provides processing of information on the medical device 232 for the dispensing of the beneficial agent. The CPU 270 is initially programmed with the manufacturing specifications as to the size, shape and arrangement of the openings in the medical device 232. A keyboard 272 is preferably used to assist with the loading of the CPU 270 and for input of information relating to the loading process.

[0073] The medical devices 232 are preferably affixed to the mandrel 230 and mapped prior to the loading process. The mapping process allows the observation system and associated control system to determine a precise location of each of the openings which may vary slightly from device to device and mandrel to mandrel due to inaccuracies of loading the devices on the mandrels. This precise location of each of the openings is then saved as the specific map for that specific mandrel.

The mapping of the mandrel 230 is performed by using the observation system to ascertain the size, shape and arrangement of the openings of each medical device 232 located on the mandrel 230. Once the mandrel 230 including the plurality of medical devices 232 have been mapped, the mapping results are compared to the manufacturing specifications to provide adjustments for the dispenser to correctly dispense the beneficial agent into each of the holes of the medical device 232.

[0074] In an alternative embodiment, the mapping of the mandrel 230 is performed on an opening by opening comparison. In operation, the observation system maps a first opening in the medical device and compares the mapping result to the manufacturing specifications. If the first opening is positioned as specified by the manufacturing specifications, no adjustment is needed. However, if the first opening is not positioned as specified by the manufacturing specifications, an adjustment is recorded and an adjustment is made during the dispensing process to correct for the position which is different than as specified in the manufacturing specifications. The mapping is repeated for each opening of the medical device until each medical device 232 has been mapped. In addition, in one embodiment, if an opening is mapped and the opening is positioned pursuant to the manufacturing specifications, the mapping process can be designed to proceed to map at every other opening or to skip any number of openings without departing from the present invention.

[0075] After the mandrel has been mapped, the medical device 232 is filled with the beneficial agent based on the manufacturers' specification and adjustments from the mapping results. The CPU provides the programmed data for filling of each medical device 232. The programmed data includes the medical device design code, date created, lot number being created, number of medical devices 232 on the mandrel, volume of each opening in the medical device 232, different

beneficial agents to be loaded or dispensed into the openings in the medical device 232, the number of layers, drying/baking time for each layer, and any other data.

[0076] In one embodiment, the medical device 232 will have at least 10 beneficial agent layers which will be filled including at least one barrier layer, at least one therapeutic layer having a beneficial agent, and at least one cap layer. The beneficial agent layers may include layers which vary in concentration and strength of each solution of drug or therapeutic agent, amount of polymer, and amount of solvent.

[0077] In operation, the operator will input or scan the bar code 234 of the mandrel into the CPU 270 before the filling process begins. The initial filling generally includes a mixture of polymer and solvent to create a barrier layer. Each of the openings are typically filled to about 80% capacity and then the mandrel is removed from the system and placed into an oven for baking. The baking process evaporates the liquid portion or solvent from the openings leaving a solid layer. The mandrel is typically baked for about 60 minutes plus or minus 5 minutes at about 55 degrees C. To assist in error prevention, the CPU software receives the bar code of the mandrel and will not begin filling the second layer until at least 60 minutes since the last filling. The second layer and subsequent layers are then filled in the same manner as the first layer until the opening has been filled to the desired capacity. The reservoir 218 can also be bar coded to identify the solution in the reservoir.

[0078] The observation system 220 also can verify that the dispenser 210 is dispensing the beneficial agent into the openings through either human observation on the monitor 270 or via data received from the observation system and conveyed to the CPU to confirm the dispensing of the beneficial agent in the openings of the medical device 232. Alternatively, refraction of a light beam can be used to count droplets dispensed at a high speed.

[0079] The dispensers 100 run very consistently for hours at a time, but will drift from day to day. Also, any small change in the waveform will change the drop size. Therefore, the output of the dispenser 100 can be calibrated by firing a known quantity of drops into a cup and then measuring the amount of drug in the cup. Alternatively, the dispenser 100 can be fired into a cup of known volume and the number of drops required to exactly fill it can be counted.

[0080] In filling the openings of the medical device 232, the micro-jetting dispenser 100 dispenses a plurality of droplets into the opening. In one preferred embodiment, the dispenser is capable of dispensing 3000 shots per second through a micro-jetting dispenser of about 40 microns. However, the droplets are preferably dispensed at between about 8 to 20 shots per hole depending on the amount of fill required. The micro-jetting dispenser fills each hole (or the holes desired) by proceeding along the horizontal axis of the medical device 232. The CPU 270 turns the dispenser 100 on and off to fill the openings substantially without dispensing liquid between openings on the medical device. Once the dispenser has reached an end of the medical device 232, the means for rotating the mandrel rotates the mandrel and a second passing of the medical device 232 along the horizontal axis is performed. In one embodiment, the medical devices 232 are stents having a diameter of about 3 mm and a length of about 17 mm and can be filled in about six passes. Once the medical device 232 is filled, the dispenser 210 moves to the next medical device 232 which is filled in the same manner.

[0081] The CPU 270 insures that the mandrel is filled accurately by having safety factors built into the filling process. It has also been shown that by filling the openings utilizing a micro-jetting dispenser, the amount of drugs or therapeutic agent used is substantially less than coating the medical device 232 using previously known method including spraying or dipping. In addition, the micro-jetting of a beneficial agent provides an improved work environment by exposing

the worker to a substantially smaller quantity of drugs than by other known methods.

[0082] The system 200 also includes an electrical power source 290 which provides electricity to the piezoelectric micro-jetting dispenser 210.

[0083] The medical devices 232 can be removed from the mandrel by expanding the devices and sliding them off the mandrel. In one example, stents can be removed from the mandrel by injecting a volume of air between the outer diameter of the wire member 162 and the inner diameter of the outer jacket. The air pressure causes the medical device 232 to expand such that the inner diameter of the medical device 232 is greater than the outer diameter of the mandrel. In one embodiment, a die is place around the mandrel to limit the expansion of the medical device 232 as the air pressure between the outer diameter of the wire member 162 and the inner diameter of the outer jacket 164. The die can be constructed of stainless steel or plastics such that the medical devices 232 are not damaged during removal from the mandrel. In addition, in a preferred embodiment, the medical devices 232 are removed four at a time from the mandrel. A 12-inch mandrel will accommodate about 11, 3 mm by 17 mm medical devices having approximately 597 openings.

[0084] FIG. 7 illustrates one embodiment of a dispenser 300 which precisely delivers droplets by acoustic droplet ejection. The dispenser 300 includes an accoustic energy transducer 310 in combination with a replaceable fluid reservoir 320. The dispenser 300 releases a nanoliter or picoliter droplet from a surface of the liquid in the reservoir 320 accurately into an opening in the medical device 140 positioned in the path of the droplet.

[0085] The dispenser 300 operates by focusing acoustic energy from the transducer 310 through a lens onto the surface of the fluid in the reservoir 320. The fluid then creates a mound at the surface which erupts and releases a droplet

of a controlled size and trajectory. One example of a system for focusing the acoustic energy is described in U.S. Patent No. 6,548,308 which is incorporated herein by reference. The medical device 140 and mandrel 164 may be moved or the dispenser 300 may be moved to precisely control the dispensing of the droplets into the openings in the medical device.

[0086] Some of the advantages of the use of an acoustic dispenser 300 include the ability to deliver more viscous fluids and the ability to deliver volatile fluids containing solvents. For example, the fluids delivered by the dispenser 300 can have a viscosity of greater than about 40 centipoise. The delivery of more viscous materials allows the use of higher solids content in the delivered fluid and thus, fewer layers. The droplet volume when using the dispenser 300 is a function of the fluid and transducer driving parameters and can range from about 1 picoliter to about 50 nanoliters per droplet.

[0087] The dispenser 300 also has the advantage of simple and fast transfer between dispensed liquids since the reservoir is self contained and the parts do not require cleaning. In addition, no loss of drug occurs when switching between drugs.

[0088] The acoustic dispenser 300 delivers the droplet in a straight trajectory without any interference from the side walls of the reservoir 320. The straight trajectory of the fluid droplets allows the dispenser 300 to operate accurately spaced away from the medical device to allow improved visualization.

[0089] FIG. 8 illustrates an alternative embodiment of a reservoir 400 for an acoustic dispenser which can deliver compositions containing volatile solvents. The reservoir 400 includes a vapor chamber 410 above the fluid chamber 420. The vapor chamber 410 retains evaporated solvent vapor and reduces the rapid evaporation rate of the volatile solvents by providing a high concentration of solvent vapor at the surface of the liquid.

[0090] The dispenser 500 of FIG. 9 uses a solvent cloud formation system to surround a dispenser 510, such as the piezoelectric dispenser of FIG. 3, with a cloud of the same solvent used in the dispensed fluid to reduce solvent evaporation and fowling of the dispenser tip. In the FIG. 9 example, the solvent cloud is created by a ring 520 of porous material, such as porous metal, through which the solvent is delivered by a feed line 530 from an auxiliary solvent source. The solvent evaporating from the porous material ring 520 creates a cloud of solvent directly around the dispenser tip. The creation of a solvent cloud around a dispenser tip reduces the solvent vapor concentration differential near the tip of the dispenser. Lowering this differential will increase the time that the dispenser can be left idle without clogging due to solvent evaporation. This improves the robustness of the process.

Example 1

[0091] In the example below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

DMSO = Dimethyl Sulfoxide

IV = Inherent Viscosity

PLGA = poly(lactide-co-glycolide)

<u>TABLE I</u>			
<u>Solutions</u>	<u>Drug</u>	<u>Polymer</u>	<u>Solvent</u>
A	None	4% PLGA 50/50 IV=0.82	DMSO
DA	0.64% paclitaxel	8% PLGA 50/50 IV=0.59	DMSO
DA	0.64% paclitaxel	8% PLGA 50/50 IV=0.60	DMSO
DD	0.14% paclitaxel	8% PLGA 50/50 IV=0.59	DMSO
L	None	8% PLGA 50/50 IV=0.59	DMSO

<u>TABLE II</u>		
<u>Layer No.</u>	<u>Solution</u>	<u>Layer No., this Solution</u>
1	A	1
2	A	2
3	A	3
4	A	4
5	A	5
6	A	6
7	A	7
8	A	8
9	A	9
10	DA	1
11	DA	2
12	DD	1
13	L	1

[0092] A plurality of medical devices, preferably 11 medical devices per mandrel are placed onto a series of mandrels. Each mandrel is bar coded with a unique indicia which identifies at least the type of medical device, the layers of beneficial agents to be loaded into the opening of the medical devices, and a specific identity for each mandrel. The bar code information and the mapping results are stored in the CPU for loading of the stent.

[0093] A first mixture of poly(latide-co-glycolide) (PLGA) (Birmingham Polymers, Inc.), and a suitable solvent, such as DMSO is prepared. The mixture is loaded by droplets into holes in the stent. The stent is then preferably baked at a

temperature of 55 degrees C for about 60 minutes to evaporate the solvent to form a barrier layer. A second layer is laid over the first by the same method of filling polymer solution into the opening followed by solvent evaporation. The process is continued until 9 individual layers have been loaded into the openings of the medical device to form the barrier layer.

[0094] A second mixture of paclitaxel, PLGA, and a suitable solvent such as DMSO forming a therapeutic layer is then introduced into the openings of the medical device over the barrier layer. The solvent is evaporated to form a drug filled protective layer and the filling and evaporation procedure repeated until the hole is filled until the desired amount of paclitaxel has been added to the openings of the medical device.

[0095] A third mixture of PLGA and DMSO is then introduced into the openings over the therapeutic agent to form a cap layer. The solvent is evaporated and the filling and evaporation procedure repeated until the cap layer has been added to the medical device, in this embodiment, a single cap layer has been added.

[0096] In order to provide a plurality of layers of beneficial agents having a desired solution, the reservoir is replaced and the piezoelectric micro-jetting dispenser is cleaned. The replacement of the reservoir and cleaning of the dispenser (if necessary) insures that the different beneficial layers have a desired solution including the correct amount of drugs, solvent, and polymer.

[0097] Following implantation of the filled medical device *in vivo*, the PLGA polymer degrades via hydrolysis and the paclitaxel is released.

[0098] While the invention has been described in detail with reference to the preferred embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made and equivalents employed, without departing from the present invention.